1: Br J Cancer. 2003 Oct 6;89(7):1248-54.

BJC British Journal of Cancer

# Seroprevalence of human papillomavirus-16, -18, -31, and -45 in a population-based cohort of 10 000 women in Costa Rica.

**Wang SS, Schiffman M, Shields TS, Herrero R, Hildesheim A, Bratti MC, Sherman ME, Rodriguez AC, Castle PE, Morales J, Alfaro M, Wright T, Chen S, Clayman B, Burk RD, Viscidi RP.**

1National Cancer Institute, Bethesda, MD 20892-7234, USA.

Human papillomavirus (HPV) seroprevalence and determinants of seropositivity were assessed in a 10 049-woman population-based cohort in Guanacaste, Costa Rica. Serologic responses based on VLP-based ELISA were obtained from the plasma collected at study enrollment in 1993/1994 for HPV-16 (n=9949), HPV-18 (n=9928), HPV-31 (n=9932), and HPV-45 (n=3019). Seropositivity was defined as five standard deviations above the mean optical density obtained for studied virgins (n=573). HPV-16, -18, -31, and -45 seroprevalence was 15, 15, 16, and 11%, respectively. Of women DNA-positive for HPV-16, -18, -31, or -45, seropositivity was 45, 34, 51, and 28%, respectively. Peak HPV seroprevalence occurred a decade after DNA prevalence; lifetime number of sexual partners was the key determinant of seropositivity independent of DNA status and age. DNA- and sero-positive women showed the highest risk for concurrent CIN3/cancer, followed by DNA-positive, sero-negative women.British Journal of Cancer (2003) 89, 1248-1254. doi:10.1038/sj.bjc.6601272 www.bjcancer.com

PMID: 14520455 [PubMed - in process]

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L3: Entry 1 of 1 File: USPT May 21, 2002

DOCUMENT-IDENTIFIER: US 6391539 B1
TITLE: Immunogenic compositions of human papillomavirus

US Patent No. (1):
6391539

Detailed Description Text (38):
The invention equally concerns serums susceptible to being obtained by immunization of a mammal, which may be used for the preparation of administrable in effective doses to a patient, notably parenterally, these serums then being able to provoke a remission of the infections induced by the corresponding types or sub-types of papillomaviruses.

CLAIMS:

6. A method of preparing a serum for inducing an immune response against an infection of human papillomavirus, comprising immunizing a mammal with an immunogenic composition according to claim 1, 2, or 3, wherein the mammal produces the serum in response to immunization with the immunogenic composition.

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**Search Results** - Record(s) 1 through 4 of 4 returned.

☐ 1. Document ID: US 6479258 B1

L3: Entry 1 of 4 File: USPT Nov 12, 2002

US-PAT-NO: 6479258
DOCUMENT-IDENTIFIER: US 6479258 B1

TITLE: Non-stochastic generation of genetic vaccines

DATE-ISSUED: November 12, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Short; Jay M. | Rancho Santa Fe | CA | | |

US-CL-CURRENT: 435/69.1; 530/350, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 6365160 B1

L3: Entry 2 of 4 File: USPT Apr 2, 2002

US-PAT-NO: 6365160
DOCUMENT-IDENTIFIER: US 6365160 B1

TITLE: Papillomavirus polyprotein constructs

DATE-ISSUED: April 2, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Webb; Elizabeth Ann | Eltham | | | AU |
| Margetts; Mary Brigid | Moonee Ponds | | | AU |
| Cox; John Cooper | Bullengarook | | | AU |
| Frazer; Ian | St. Lucia | | | AU |
| McMillan; Nigel Alan John | Woollongabba | | | AU |
| Williams; Mark Philip | Annerley | | | AU |
| Moloney; Margaret Bridget Holland | Essendon | | | AU |
| Edwards; Stirling John | Coburg | | | AU |

US-CL-CURRENT: 424/192.1; 424/186.1, 424/199.1, 424/204.1, 435/235.1, 435/320.1, 435/69.1, 435/69.7, 530/350, 536/23.72

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 3. Document ID: US 5855891 A

L3: Entry 3 of 4 File: USPT Jan 5, 1999

US-PAT-NO: 5855891
DOCUMENT-IDENTIFIER: US 5855891 A

TITLE: Ichimeric papillomavirus-like particles

DATE-ISSUED: January 5, 1999

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Lowy; Douglas R. | Bethesda | MD | | |
| Schiller; John T. | Silver Spring | MD | | |
| Greenstone; Heather | Silver Spring | MD | | |

US-CL-CURRENT: 424/192.1; 424/204.1, 435/235.1, 435/236, 435/69.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 4. Document ID: US 5618536 A

L3: Entry 4 of 4 File: USPT Apr 8, 1997

US-PAT-NO: 5618536
DOCUMENT-IDENTIFIER: US 5618536 A

TITLE: Chimeric papillomavirus-like particles

DATE-ISSUED: April 8, 1997

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Lowy; Douglas R. | Bethesda | MD | | |
| Schiller; John T. | Silver Spring | MD | | |
| Greenstone; Heather | Silver Spring | MD | | |

US-CL-CURRENT: 424/192.1; 424/204.1, 435/235.1, 435/236, 435/254.2, 435/317.1, 435/320.1, 435/325, 435/348, 435/69.1, 435/69.3, 530/412, 530/413, 536/23.4, 536/23.72

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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| Terms | Documents |
|---|---|
| HPV-31 and serum antibody | 4 |

d 13 9 all

L3 ANSWER 9 OF 18 MEDLINE on STN
AN 1999445605 MEDLINE
DN 99445605 PubMed ID: 10515799
TI Seroreactivity to human papillomavirus types 16, 18, 31, and 45 virus-like particles in a case-control study of cervical squamous intraepithelial lesions.
AU Wideroff L; Schiffman M; Haderer P; Armstrong A; Greer C E; Manos M M; Burk R D; Scott D R; Sherman M E; Schiller J T; Hoover R N; Tarone R E; Kirnbauer R
CS NCI/ARB, EPN 313 MSC 7344, Bethesda, MD 20892-7344, USA.. wideroff@nih.gov
SO JOURNAL OF INFECTIOUS DISEASES, (1999 Nov) 180 (5) 1424-8.
Journal code: 0413675. ISSN: 0022-1899.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991209
AB Serum IgG **antibodies** to human papillomavirus (HPV) types 16, 18, 31, and 45 virus-like particles were measured in a nested case-control study of cervical squamous intraepithelial lesions. HPV-16 seroreactivity was strongly associated with HPV-16 DNA detection (odds ratio, 9.0; 95% confidence interval, 4.4-19.4), and similar type specificity was observed for **HPV-31** and -45. In contrast, seroreactivity to any type was associated with elevated seroreactivity to all others. Among cases and controls, HPV-16 showed the highest seroprevalence, with 23.8% of 80 cases and 10.5% of 258 controls seroreactive to HPV-16 alone, and another 27.5% and 5.4%, respectively, seroreactive to HPV-16 plus other types. Overall, 24 (30.0%) cases and 17 (6.6%) controls were seroreactive to multiple types. These data suggest that seroreactivity to a given type reflects mainly type-specific HPV infection as measured by DNA detection and may also signal past exposure to other types that are now only serologically detected.
CT Check Tags: Female; Human; Support, Non-U.S. Gov't
***Antibodies, Viral: BL, blood**
Case-Control Studies
*Cervical Intraepithelial Neoplasia: VI, vi

# WEST Search History

DATE: Tuesday, October 07, 2003

| Set Name side by side | Query | Hit Count | Set Name result set |
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| L13 | Orth Gerard.in. | 14 | L13 |
| *DB=JPAB; PLUR=YES; OP=ADJ* | | | |
| L12 | HPV adj 31 and serum | 0 | L12 |
| *DB=EPAB; PLUR=YES; OP=ADJ* | | | |
| L11 | HPV adj 31 and serum | 0 | L11 |
| *DB=PGPB; PLUR=YES; OP=ADJ* | | | |
| L10 | HPV adj 31 and serum.clm. | 1 | L10 |
| L9 | HPV adj 31 and serum | 24 | L9 |
| *DB=DWPI; PLUR=YES; OP=ADJ* | | | |
| L8 | HPV adj 31 and serum | 2 | L8 |
| *DB=USPT; PLUR=YES; OP=ADJ* | | | |
| L7 | HPV adj 31 and serum.clm. | 2 | L7 |
| L6 | HPV adj 31 and serum | 61 | L6 |
| L5 | HPV adj 31.clm. | 19 | L5 |
| L4 | HPV adj 31 | 79 | L4 |
| L3 | L2 and serum | 1 | L3 |
| L2 | 6391539.pn. | 1 | L2 |
| L1 | 5876922.pn. | 1 | L1 |

END OF SEARCH HISTORY

d 19 1-3

L9 ANSWER 1 OF 3 MEDLINE on STN
AN 95264502 MEDLINE
DN 95264502 PubMed ID: 7745754
TI Immunization with viruslike particles from cottontail rabbit **papillomavirus** (CRPV) can protect against experimental CRPV infection.
AU Breitburd F; Kirnbauer R; Hubbert N L; Nonnenmacher B; Trin-Dinh-Desmarquet C; **Orth G**; Schiller J T; Lowy D R
CS Unite des papillomavirus, Institut National de la Sante et de la Recherche Medicale U-190, Institut Pasteur, Paris, France.
SO JOURNAL OF VIROLOGY, (1995 Jun) 69 (6) 3959-63.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199506
ED Entered STN: 19950621
Last Updated on STN: 19950621
Entered Medline: 19950613

L9 ANSWER 2 OF 3 MEDLINE on STN
AN 91284193 MEDLINE
DN 91284193 PubMed ID: 1647881
TI Constitutive release of IL6 by human **papillomavirus** type 16 (HPV16)-harboring keratinocytes: a mechanism augmenting the NK-cell-mediated lysis of HPV-bearing neoplastic cells.
AU Malejczyk J; Malejczyk M; Urbanski A; Kock A; Jablonska S; **Orth G** ; Luger T A
CS Department of Histology and Embryology, Warsaw Medical School, Poland.
SO CELLULAR IMMUNOLOGY, (1991 Aug) 136 (1) 155-64.
Journal code: 1246405. ISSN: 0008-8749.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199108
ED Entered STN: 19910825
Last Updated on STN: 19910825
Entered Medline: 19910808

L9 ANSWER 3 OF 3 MEDLINE on STN
AN 89138700 MEDLINE
DN 89138700 PubMed ID: 2537261
TI Abrogated NK-cell lysis of human **papillomavirus** (HPV)-16-bearing keratinocytes in patients with pre-cancerous and cancerous HPV-induced anogenital lesions.
AU Malejczyk J; Majewski S; Jablonska S; Rogozinski T T; **Orth G**
CS Department of Histology and Embryology, Warsaw Medical School, Poland.
SO INTERNATIONAL JOURNAL OF CANCER, (1989 Feb 15) 43 (2) 209-14.
Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198903
ED Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890327

=> d l9 1-3 ab

L9 ANSWER 1 OF 3 MEDLINE on STN

AB We tested the ability of vaccination with virus-like particles (VLPs) to protect domestic rabbits against papillomas induced by the cottontail rabbit **papillomavirus** (CRPV). A recombinant baculovirus system that expressed only the L1 major **papillomavirus** structural protein or L1 plus the minor L2 protein was used in insect cells as the source of VLPs. Groups of 10 rabbits were immunized with native or denatured VLPs from CRPV or type 1 bovine **papillomavirus** by using Freund's adjuvant. Alum was used as the adjuvant for an additional group immunized with CRPV L1-L2 VLPs. Animals were challenged with 5 x 10(10) and 2 x 10(11) particles on opposing flanks. No protection was seen in rabbits immunized with native or denatured bovine **papillomavirus** L1-L2 or with denatured CRPV L1-L2. In these groups, the lower and higher challenge doses resulted in 27 of 30 animals with extensive papillomas, with each of the remaining animals having a smaller number of persistent papillomas. Progression to carcinoma developed in 20 rabbits. Animals inoculated with native CRPV VLPs composed of L1 alone or L1-L2 developed many fewer lesions; the lower and higher challenge doses resulted in 17 of 29 and 5 of 29 rabbits, respectively, with no lesions, and the remainder developed only one to eight papillomas, which all regressed except for those on 1 rabbit. None developed cancer within 1 year of infection. Rabbits vaccinated with native CRPV VLPs developed high-titer antibodies in an enzyme-linked immunosorbent assay based on native VLPs, and passive transfer of **serum** or immunoglobulin G from rabbits immunized with CRPV VLPs protected against CRPV challenge. We conclude that native VLPs can induce antibody-mediated, type-specific protection against experimental **papillomavirus** infection.

L9 ANSWER 2 OF 3 MEDLINE on STN

AB In the present study we demonstrate that the cultured human keratinocyte cell line (SK-v cells) harboring and expressing integrated human **papillomavirus** type 16 (HPV16) DNA sequences constitutively releases IL6, which is known as a pleiotropic immunoregulatory cytokine of potential antitumor properties. The presence of IL6 activity in SK-v cell-conditioned media (SK-v CM) was demonstrated by tritiated thymidine incorporation into IL6-dependent B9 murine plasmacytoma cells. The effect on B9 cells was specific since it could be inhibited by anti-IL6 neutralizing antibodies but not by a normal control **serum**. IL6 did not affect SK-v cell growth; however, it significantly augmented NK cell activity of human peripheral blood lymphocytes against both K562 erytholeukemic and SK-v cells as assessed by 51Cr release assay. SK-v CM displayed NK cell-augmenting activity that copurified with IL6 activity in both size exclusion and anion-exchange HPLC. Furthermore, SK-v cell-derived NK cell stimulatory activity could be neutralized with anti-IL6 antibodies. These results suggest that HPV-harboring neoplastic cells can release IL6 which may indirectly mediate tumor death by augmentation of NK cell activity.

L9 ANSWER 3 OF 3 MEDLINE on STN

AB Natural-cell-mediated cytotoxicity against K-562 erythroleukemic cells and human **papillomavirus** (HPV)-16 harboring Sk-v keratinocytes was tested in 38 age- and sex-matched healthy volunteers and in patients with HPV-induced benign and malignant anogenital lesions: 9 persons with HPV-16-induced bowenoid papulosis (BP), 8 with anogenital carcinomas (5 with HPV-16- or 33-associated squamous-cell carcinomas of Bowen's type and 3 with HPV-6-associated Buschke-Loewenstein verrucous carcinomas) and 12 with HPV-6-induced condylomata acuminata. Both K-562 and Sk-v cells were killed by a non-adherent CD16+ subset of PBMC as revealed by cell

fractionation on the basis of their adherence to plastic and by treatment with Leu-IIb monoclonal antibody (MAb) and complement. "Cold" target competitive assays demonstrated that both cell types inhibited lysis of labelled Sk-v cells. In patients with BP and anogenital carcinomas induced by HPV-16 or 33, there was a significant (at least at p less than 0.01) decrease of Sk-v cell lysis as compared with the healthy control group. Anti-K-562 activity was not affected. In patients with anogenital carcinomas the degree of Sk-v lysis was decreased in proportion to the duration of lesions (correlation coefficient-r = -0.79). Neither anti-K-562 nor anti-Sk-v cytotoxicities were significantly affected in patients with condylomata and with HPV-6 associated verrucous carcinomas. Short-term (3 hr) pre-incubation of normal PBMC with sera from patients with BP and HPV-16-associated anogenital carcinomas resulted in significant inhibition of their ability to lyse Sk-v cells. Lysis of K-562 cells remained unaffected. In patients with carcinomas, the suppressive effect of sera was associated with a lowering of the ability of their PBMC to lyse Sk-v cells (r = -0.79). In patients with longer tumor persistence, the suppressive effect of **serum** was proportionally higher (r = 0.86).

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     (FILE 'HOME' ENTERED AT 14:20:55 ON 07 OCT 2003)

     FILE 'MEDLINE' ENTERED AT 14:21:29 ON 07 OCT 2003
L1          1080 S HPV AND 31
L2           155 S HPV- 31
L3             2 S SERUM AND L2
               E ORTH GERARD/AU
L4             2 S E3
               E ORTH G/AU
L5           185 S E3
L6         14027 S PAPILLOMAVIRUS
L7           155 S L5 AND L6
L8             2 S HPV-31 AND L7
L9             3 S SERUM AND L7
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